

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name: A Microparticle Enzyme Immunoassay for the qualitative detection of Antibody to Hepatitis C Virus (anti-HCV)

Device Trade Name: Abbott AxSYM® Anti-HCV

Applicant's Name and Address: Abbott Laboratories
Abbott Diagnostics Division
100 Abbott Park Road
Abbott Park, Illinois 60064

Premarket Approval Application (PMA) Number: P970027

Date of Panel Recommendation: January 21, 2000

Date of Notice of Approval to the Applicant: February 5, 2004

II. INDICATIONS FOR USE

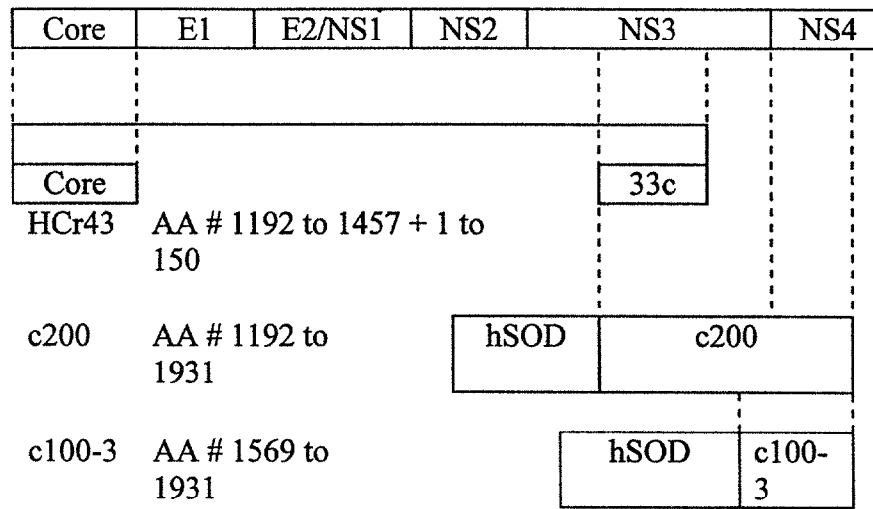
AxSYM® Anti-HCV (hepatitis C virus) is a Microparticle Enzyme Immunoassay (MEIA) for the qualitative detection of anti-HCV IgG to HCV recombinant proteins in human serum or plasma (potassium EDTA, sodium EDTA, sodium heparin, lithium heparin, sodium citrate, and potassium oxalate).

Assay results, in conjunction with other laboratory results and clinical information, may be used to provide presumptive evidence of infection with HCV virus (state of infection or associated disease not determined) in persons with signs or symptoms of hepatitis and in persons at risk for hepatitis C infection.

III. DEVICE DESCRIPTION

Abbott AxSYM® Anti-HCV (hereinafter referred to as AxSYM Anti-HCV) detects antibodies to putative structural and nonstructural proteins of the HCV genome. The relationship between the recombinant HCV proteins in AxSYM Anti-HCV and the putative structural and nonstructural proteins is depicted in the following figure.

Recombinant HCV Proteins in AxSYM Anti-HCV Polyprotein AA # 1 to 1931



* The complete HCV polyprotein contains the additional amino acids # 1932 to 3011 which are not represented in this figure.

AxSYM Anti-HCV utilizes three recombinant antigens (HCr43, c200, and c100-3) to detect anti-HCV. These antigens are used to prepare the AxSYM Anti-HCV Microparticles. All three antigens are purchased as purified proteins from Chiron® Corporation, Emeryville, California. A brief description of each is as follows:

- HCr43: The HCr43 antigen is a protein expressed in *Escherichia coli* (*E. coli*) and is composed of two noncontiguous coding regions of the Chiron HCV genome sequence. The first region represents amino acids 1192 to 1457 (33c) of the Chiron HCV sequence. The second of the two regions represent amino acids 1 to 150 (core) of the Chiron HCV sequence. Because of the similarity of the genomic organization of other flaviviruses, it is suggested that the first sequence be from the NS3 coding region and the second sequence is from the core-coding region of HCV.
- c200: The c200 antigen is a recombinant HCV protein expressed in the yeast *Saccharomyces cerevisiae*. It contains HCV amino acids 1192 to 1931 of the Chiron HCV sequence. Because of the similarity of the genomic organization of other flaviviruses, it is suggested that this sequence be from the NS3 and NS4 regions of the HCV genome. The c200 antigen is a chimeric fusion protein with 154 amino acids of human superoxide dismutase (hSOD).
- c100-3: The c100-3 antigen is a recombinant HCV protein expressed in the yeast *Saccharomyces cerevisiae*. The genomic organization of other flaviviruses suggests that the clone sequence is contained within the putative nonstructural (NS3 and NS4) regions of HCV. The c100-3 protein is a chimeric fusion protein with 154 amino acids of hSOD, five linker amino acids, amino acids number 1569 to 1931 of the HCV polyprotein, and an additional five linker amino acid chain at the carboxyl terminus.

The AxSYM Anti-HCV reagents require the use of the AxSYM System, which is cleared under 510(k) k974651. The analyzer performs all sample and reagent transfers, incubations, data processing, and completes the assay with a printed report.

The sample and all AxSYM Anti-HCV reagents required for one test are pipetted by the Sampling Probe into various wells of a reaction vessel (RV) in the Sampling Center. The RV is immediately transferred into the Processing Center. The Processing Probe performs further pipetting steps in the Processing Center.

The reactions occur in the following sequence:

- Sample is diluted with Specimen Diluent 1 in one RV well and then further diluted with Specimen Diluent 2 in a second RV well.
- Recombinant HCV Antigen Coated Microparticles are added to the diluted sample. During the incubation of this reaction mixture, the anti-HCV in the sample binds to the Recombinant HCV Antigen Coated Microparticles, forming an antibody-antigen complex.
- A portion of the reaction mixture is transferred to the matrix cell. The microparticles bind irreversibly to the glass fiber matrix.
- The matrix cell is washed to remove materials not bound to the microparticles.
- Anti-Human IgG (Goat): Alkaline Phosphatase Conjugate is dispensed onto the matrix cell. During the incubation of this reaction mixture, the Anti-Human IgG (Goat): Alkaline Phosphatase Conjugate binds to the antibody-antigen complex.
- The matrix cell is washed to remove materials not bound to the microparticles.
- The substrate, 4-methylumbelliferyl phosphate, is added to the matrix cell. The alkaline phosphatase-labeled conjugate catalyzes the removal of a phosphate group from the substrate, yielding the fluorescent product, 4-methylumbelliferone. The MEIA optical assembly measures this fluorescent product.

The presence or absence of anti-HCV in the sample is determined by comparing the rate of formation of fluorescent product to the cut-off rate, which is calculated from a previous AxSYM Anti-HCV Index Calibration. If the rate of formation of fluorescent product in the sample is greater than or equal to the cut-off rate, the sample is considered reactive for anti-HCV.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

There are no known contraindications for the AxSYM Anti-HCV assay.

Warnings and Precautions for the AxSYM Anti-HCV assay are stated in the product labeling.

V. ALTERNATE PRACTICES AND PROCEDURES

Determining the presence of anti-HCV in patients may be achieved by using a variety of commercially available, FDA-approved serological tests. When these tests results are used in combination with a physician's assessment and other laboratory test results, infection with HCV can be identified.

VI. MARKETING HISTORY

This product (AxSYM Anti-HCV, List No. 5C36) has not been marketed in any other country. Two similar assays (AxSYM HCV version 3.0, List No. 3B44 and AxSYM Abbott HCV, List No. 1D30) are manufactured and marketed in the following countries outside the United States since 1997.

Algeria	El Salvador	Malta	Slovakia
Argentina	Estonia	Mauritius	Slovenia
Australia	Finland	Mexico	South Africa
Austria	France	Morocco	South Korea
Bahrain	Germany	Namibia	Spain
Belarus	Greece	Netherlands	Sweden
Belgium	Guam / Saipan	New Zealand	Switzerland
Bosnia / Herzegovina	Guatemala	North Cypress	Syria
Brazil	Honduras	North Yemen	Taiwan
Bulgaria	Hungary	Norway	Thailand
Canada	India	Oman	Tunisia
Chile	Indonesia	Pakistan	Turkey
China	Ireland	Panama	U.A.B.
C.I.S.	Israel	Paraguay	U.A.E. (Dubai)
Columbia	Italy	Peru	Ukraine
Costa Rica	Ivory Coast	Philippines	United Kingdom
Croatia	Japan	Poland	Uruguay
Curacao	Jordan	Portugal	Venezuela
Cyprus	Kenya	Qatar	Vietnam
Czech Republic	Kuwait	Romania	Yugoslavia
Denmark	Latvia	Saudi Arabia	Zimbabwe
Dominican Republic	Lebanon	Senegal	
Ecuador	Lithuania	Serbia	
Egypt	Malaysia	Singapore	

The devices have not been withdrawn from any of these countries for reasons related to safety and effectiveness of the device.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

There are no known potential direct adverse effects of this device on the health of the user if the device is used according to the instructions in the package insert. However, failure of the test to perform as indicated or human error during performance of the test may lead to a false diagnosis and improper patient management.

A false positive result using an anti-HCV assay is not considered a patient or public health concern since a reactive EIA results in a clinical lab should be followed up with supplemental tests (e.g., strip immunoblot assay (SIA) and/or PCR for detection of HCV RNA) to determine inactive or resolved infection versus active HCV replication. Treatment of the patient with chronic HCV infection is initiated only after extensive clinical, laboratory and behavioral assessment of the patient (e.g., elevated ALT levels for six months, detectable serum HCV RNA, liver biopsy with portal fibrosis, patient compliance, and abstinence from drugs and alcohol).

A false negative anti-HCV result in a diagnostic setting may lead to a patient with HCV going unidentified. Under these circumstances, there is a safety concern for both the patient and the public, since such individuals may be capable of transmitting HCV infection. However, if a patient is known to be at high risk of HCV infection, or is symptomatic, and the physician's suspicion of HCV infection is high, HCV RNA testing is often employed and is of diagnostic value, even after an initial negative anti-HCV test result.

VIII. SUMMARY OF NON CLINICAL STUDIES

The applicant performed in-house studies in order to evaluate the following performance characteristics of the AxSYM Anti-HCV assay: Cut-off determination and verification, sample handling and collection, interference, sample carryover, and stability.

Cut-off Determination and Verification

The cut-off value was selected in order to have an appropriate assay cut-off that would result in optimal specificity while maintaining acceptable sensitivity for AxSYM Anti-HCV. In order to select the preliminary cut-off, data obtained from the in-house studies (n = 1,262) and (n = 146) were evaluated. The preliminary cut-off was then challenged or verified during the clinical studies (n = 2,209) and (n = 679).

The cut-off for AxSYM Anti-HCV is described as a fraction of the Index Calibrator (IC) rate. The sponsor conducted studies to determine the optimal IC multiplication factor to be used for calculating the cut-off rate.

Receiver-operating characteristic (ROC) analysis was used to assist in the determination and verification of the AxSYM Anti-HCV assay cutoff. The cut-off was verified by ROC analysis after re-categorization of clinical specimens and expressed as follows:

Cut-off Rate (CO) = 0.12 Index Calibrator mean rate

Assay results are expressed as the ratio of the sample rate to the cut-off rate. The following AxSYM Anti-HCV result calculation is used:

$S/CO = \text{Sample Rate (S)} / \text{Cut-off Rate (CO)}$

Clinical Sample Types (Serum and Plasma)

The sponsor conducted a study using the AxSYM Anti-HCV assay to determine if there was any difference in results when using plasma specimens or serum specimens.

Data obtained demonstrated that there were no statistically significant differences and support the use of the AxSYM Anti-HCV assay with serum specimens collected in serum tubes or serum separator tubes, and plasma specimens collected in the following anticoagulants: potassium EDTA, sodium EDTA, sodium heparin, lithium heparin, sodium citrate, and potassium oxalate.

Sample Freeze/Thaw

The sponsor conducted studies to assess the performance of AxSYM Anti-HCV with plasma specimens that have undergone multiple freeze/thaw cycles.

Data obtained support the use of the AxSYM Anti-HCV assay with specimens that have undergone up to six freeze/thaw cycles.

Sample Heat Inactivation

The sponsor conducted a study to assess the performance of the AxSYM Anti-HCV assay with plasma specimens that have been heat-inactivated.

The data do not support the use of the AxSYM Anti-HCV assay with specimens that have been heat-inactivated at 56°C. This information is provided in the Sample collection and Preparation for Analysis section of the labeling.

“Off the Cells” Sample Shipping/Storage Conditions

A study was conducted to assess the performance of the AxSYM Anti-HCV assay with plasma specimens after removal from the collection tubes (*i.e.*, “off the cells”) subjected to various shipping/storage conditions.

The data support the use of the AxSYM Anti-HCV assay with specimens that have been stored off the cells at the following conditions: 2 to 8°C for 28 days; 15 to 30°C for 14 days; 37°C for 3 days.

The data do not support the use of the AxSYM Anti-HCV assay with specimens that have been stored off the cells at 45°C. This information is provided in the Sample collection and Preparation for Analysis section of the labeling.

“On the Cells” Sample Shipping/Storage Conditions

The sponsor conducted a study to assess the performance of the AxSYM Anti-HCV assay with plasma specimens stored in the original collection tubes (*i.e.*, “on the cells”) subjected to various shipping/storage conditions.

The data support the use of the AxSYM Anti-HCV assay with specimens that have been stored on the cells at the following conditions: 2 to 8°C for 28 days; 15 to 30°C for 14 days; and 37°C for 7 days.

The data do not support the use of the AxSYM Anti-HCV assay with specimens that have been stored on the cells at 45°C. This information is provided in the Sample collection and Preparation for Analysis section of the labeling.

Potentially Interfering Substances (Triglycerides)

The sponsor conducted a study to assess the performance of the AxSYM Anti-HCV assay to determine the potential interference associated with use of specimens containing various levels (30 to 3,000 mg/dL) of triglycerides. Expected serum or plasma levels of triglycerides in an apparently healthy, fasting adult population can range from 30 to 220 mg/dL.

The data support the use of the AxSYM Anti-HCV assay with specimens that contain up to 3,000 mg/dL of triglycerides.

Potentially Interfering Substances (Total Protein)

The sponsor conducted a study to assess the performance of the AxSYM Anti-HCV assay to determine the potential interference associated with use of specimens containing various levels (6.1 to 12.0 g/dL) of total protein. Expected serum or plasma levels of total protein in an apparently healthy population can range from 6.4 to 8.2 g/dL.

The data support the use of the AxSYM Anti-HCV assay with specimens that contain up to 12 g/dL of total protein.

Potentially Interfering Substances (Total Bilirubin)

The sponsor conducted a study using the AxSYM Anti-HCV assay to assess the potential assay interference associated with use of specimens containing various levels (< 0.2 to 20 mg/dL) of total bilirubin. Expected levels of total bilirubin in an apparently healthy, adult population can range from 0.2 to 1.2 mg/dL.

The data support the use of the AxSYM Anti-HCV assay with specimens that contain up to 20 mg/dL of total bilirubin.

Potentially Interfering Substances (Hemoglobin)

The sponsor conducted a study to assess the AxSYM Anti-HCV assay for potential interference associated with use of specimens containing various levels (0 to 500 mg/dL) of hemoglobin. Expected serum or plasma levels of hemoglobin in an apparently healthy, adult population can range from 0 to 2.5 mg/dL.

The data support the use of the AxSYM Anti-HCV assay with specimens that contain up to 500 mg/dL of hemoglobin.

Potentially Interfering Substances (Red Blood Cells)

The sponsor conducted a study to assess the AxSYM Anti-HCV assay for potential assay interference associated with use of specimens containing various levels (0.2 to 0.4%v/v) of red blood cells.

The data support the use of the AxSYM Anti-HCV assay with specimens that contain up to 0.4%(v/v) of red blood cells.

Microbial Contamination of Specimens

The sponsor conducted a study to assess the AxSYM Anti-HCV assay for potential interference associated with specimens contaminated with microorganisms.

The data do not support the use of the AxSYM Anti-HCV assay with specimens that may have been microbially contaminated with as much as 1×10^6 CFU/mL of spores (*Bacillus subtilis*, *Candida albicans*), mold (*Aspergillus niger*), vegetative cells (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*), or an environmental isolate (*Pseudomonas fluorescens*). This is indicated in both the Warnings and Precautions section and Specimen Collection and Preparation for Analysis section of the labeling.

Sample Carryover

The sponsor conducted a study to evaluate the effect of sample carryover within the AxSYM Anti-HCV assay or from other representative AxSYM assays when processing samples that contain high levels of anti-HCV.

The data indicate that no significant sample carryover was detected within AxSYM Anti-HCV. However, AxSYM Anti-HCV is susceptible to specimen carryover from AxSYM Total T3 when a high-titer anti-HCV specimen is tested by AxSYM Total T3 and is then followed by a specimen tested by AxSYM Anti-HCV. This carryover may result in a falsely reactive AxSYM Anti-HCV result. No significant sample carryover was detected from other AxSYM assays into AxSYM Anti-HCV. This effect is stated in the Warnings and Precautions section of the labeling.

Onboard Reagent Stability

A study was conducted to determine how long the AxSYM Anti-HCV Reagent Pack can be stored onboard the AxSYM System without recalibration.

The data support the storage of the AxSYM Anti-HCV Reagent Pack onboard the AxSYM System for 336 hours without recalibration. However, to be conservative, the package insert indicates that the AxSYM Anti-HCV Reagent Pack may be on board the AxSYM System for a maximum of 112 hours.

Reagent Stability

A real-time study was conducted to demonstrate the shelf-life integrity of the AxSYM Anti-HCV Reagent Pack and Controls at the recommended storage conditions (2 to 8°C) and to demonstrate the efficacy of these reagents and controls following warehouse/shipping simulation.

The data support a shelf-life of 12 months when stored at 2 to 8°C for the AxSYM Anti-HCV Reagent Pack and 14 months for the AxSYM Anti-HCV Controls. The data also support ambient shipment of AxSYM Anti-HCV Reagent Packs and Controls based on simulated warehouse shipping/storage for 72 hours followed by 2 to 8°C storage.

Calibration Stability

A Calibration Check Panel was used to evaluate the calibration curve stability of the AxSYM Anti-HCV assay. The first run of each day was the six-member Calibration Check Panel consisting of Index Calibrator, Negative Control, Positive Control, and a supplemental panel consisting of high, medium, and low panel members. The Calibration Check Panel was tested using one reagent master lot at one clinical site for 15 working days following precision testing and then once each week until the end of the study. The AxSYM Anti-HCV calibration curve was demonstrated to be stable for up to 39 days after calibration.

Analytical Specificity (Cross-Reactivity)

In order to evaluate analytical specificity of the AxSYM Anti-HCV, one site tested a total of 200 specimens containing substances that could potentially be cross-reactive. See Table V in the Specific Performance Characteristics section of the labeling for a list of the substances tested.

One hundred eighty-four specimens were nonreactive and 15 specimens were reactive by AxSYM Anti-HCV. Thirteen (86.67%) of the 15 AxSYM Anti-HCV reactive specimens were positive for anti-HCV by the supplemental assay.

The Analytical specificity of AxSYM Anti-HCV was estimated to be 98.9% (185/187) with a 95% confidence interval of 96.2% to 99.9% by the binomial distribution.

Analytical Sensitivity

In order to evaluate analytical sensitivity, the sponsor conducted a qualitative study using a ten-member lot release panel (Antibody to Hepatitis C Virus [anti-HCV] Panel #10) obtained from the Center for Biologics Evaluation and Research (CBER).

Table I

CBER Anti-HCV Panel #10 Designation	AxSYM Anti-HCV Mean S/CO Results	AxSYM Anti-HCV Qualitative Results	Expected Qualitative Results
Member 1001	1.27	R	R or NR
Member 1002	4.86	R	R
Member 1003	0.62	NR	R or NR
Member 1004	17.07	R	R
Member 1005	2.74	R	R
Member 1006	9.50	R	R
Member 1007	6.33	R	R
Member 1008	8.54	R	R
Member 1009	10.37	R	R
Member 1010	0.36	NR	NR

R = Reactive, NR = Nonreactive

The AxSYM Anti-HCV test results agreed with the expected qualitative results provided in the anti-HCV Panel #10 data sheet.

Reproducibility

The reproducibility of AxSYM Anti-HCV was determined using the recommendations stated in the NCCLS Approved Guideline EP5-A. Three sites tested a coded 35-member panel consisting of seven unique members repeated five times within the panel. The panel was tested with one reagent master lot over a period of 20 days. Each run consisted of seven panel members tested in duplicate and two replicates each of the AxSYM Anti-HCV Negative Control (NC), Positive Control (PC), and Index Calibrator (IC). Two runs were performed daily with a minimum of 2 hours between each daily run. The total percent coefficient of variation (%CV) ranged from 7.3 to 12.2 for the anti-HCV positive panel members, from 9.4 to 10.8 for the borderline positive panel members, and from 9.1 to 14.6 for the negative panel members.

An additional study was performed to assess between-lot and between-site precision using a coded 24-member panel consisting of six unique members, four anti-HCV positive members (mean Specimen to cut-off (S/CO) ranged from 1.30 to 14.48) and two anti-HCV negative members, repeated four times within the panel. The panel was tested with three AxSYM Anti-

HCV reagent master lots twice daily for 5 days at three clinical sites. Each daily run included two replicates of the AxSYM Anti-HCV IC and the AxSYM Anti-HCV Controls. The PROC MIXED procedure in SAS® was used to estimate variance components for the mixed model. The between-lot %CV for the panel members was less than or equal to 20.0, the between-site %CV was less than or equal to 22.2, and the total %CV was less than or equal to 23.2.

Table 2

Unique Member	Panel Members	Expected Range in S/CO
A	1, 8, 21, 22, 29	11.0 to 17.0
B	2, 12, 19, 24, 35	7.0 to 10.0
C	3, 13, 17, 23, 31	4.0 to 6.0
D	4, 10, 15, 28, 32	2.0 to 4.0
E	5, 11, 16, 25, 33	0.9 to 1.1
F	6, 14, 18, 26, 34	0.5 to 0.8
G	7, 9, 20, 27, 30	0.1 to 0.4

The reproducibility of AxSYM Anti-HCV was evaluated by testing the Proficiency Panel to determine within-run, between-run, between-day, and total variability. Precision data are presented in Tables 3 through 5. The PROC MIXED procedure in SAS was utilized to produce variance components for all models. These variance components were used to create estimates of variance (standard deviation) and percent coefficient of variation (%CV) for within-run, between-run, between-day, and total. All effects were considered as random for these analyses.

The following model was used to analyze the data by site:

$$\text{Results} = \text{Day} + \text{Run (Day)} + \text{Error}$$

Where: Day is the main effect

Run is nested within each Day

Error is the Replicate or within-run effect

Note: Results are the Rate values for the Index Calibrator and S/CO values for the controls and panels.

The estimate of variance for **Total** will be the sum of the variance components for Day, Run (Day), and Error. The estimate of variance for **Between-Day** will be the variance component for Day.

The estimate of variance for **Between-Run** will be the variance component for Run (Day).

The estimate of variance for **Within-Run** will be the variance component for Error.

**Table 3 -AxSYM Anti-HCV Reproducibility
Site – Abbott Laboratories**

Panel Member	Total No. Reps	Grand Mean (S/CO)	Within-Run		Between-Run		Between-Day		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
A	80	14.21	1.019	7.2	0.000	0.0	0.214	1.5	1.042	7.3
B	80	8.75	0.593	6.8	0.259	3.0	0.000	0.0	0.647	7.4
C	80	4.77	0.358	7.5	0.129	2.7	0.000	0.0	0.380	8.0
D	80	3.12	0.322	10.3	0.000	0.0	0.052	1.7	0.326	10.4
E	80	1.04	0.093	9.0	0.000	0.0	0.062	5.9	0.112	10.8
F	80	0.65	0.053	8.1	0.000	0.0	0.030	4.6	0.061	9.3
G	80	0.23	0.022	9.5	0.009	4.0	0.004	1.8	0.024	10.4
NC	80	0.23	0.034	14.3	0.000	0.0	0.016	6.7	0.037	15.8
PC	80	4.34	0.303	7.0	0.100	2.3	0.047	1.1	0.323	7.4

Panel Member	Total No. Reps	Grand Mean (Rate)	Within-Run		Between-Run		Between-Day		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
IC	80	97.31	8.033	8.3	2.007	2.1	0.630	0.6	8.303	8.5

**Table 4 - AxSYM Anti-HCV Reproducibility
Site – J.T. Mather Memorial Hospital**

Panel Member	Total No Reps	Grand Mean (S/CO)	Within-Run		Grand Mean SD	Within -Run %CV	Between- Run SD	Between-Day %CV	Between-Day SD	Total %CV
			SD	%CV						
A	80	11.14	0.875	7.9	0.000	0.0	0.470	4.2	0.993	8.9
B	80	7.32	0.764	10.4	0.000	0.0	0.319	4.4	0.828	11.3
C	80	4.03	0.291	7.2	0.038	0.9	0.188	4.7	0.349	8.7
D	80	2.44	0.212	8.7	0.000	0.0	0.080	3.3	0.227	9.3
E	80	0.87	0.063	7.3	0.041	4.7	0.032	3.7	0.082	9.4
F	80	0.56	0.048	8.7	0.000	0.0	0.014	2.6	0.050	9.1
G	80	0.21	0.021	9.7	0.007	3.1	0.006	2.7	0.022	10.5
NC	80	0.21	0.026	12.5	0.000	0.0	0.011	5.2	0.028	13.5
PC	80	3.89	0.267	6.9	0.000	0.0	0.079	2.0	0.278	7.2

Panel Member	Total No. Reps	Grand Mean (Rate)	Within-Run		Between-Run		Between-Day		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
IC	80	90.65	8.362	9.2	0.000	0.0	1.396	1.5	8.477	9.4

Table 5
AxSYM Anti-HCV Reproducibility
Site – Sacramento Medical Foundation

Panel Member	Total No. Reps	Grand Mean (S/CO)	Within-Run		Between-Run		Between-Day		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
A	80	12.79	1.005	7.9	0.233	1.8	0.406	3.2	1.109	8.7
B	80	8.32	0.635	7.6	0.450	5.4	0.394	4.7	0.872	10.5
C	80	4.53	0.364	8.0	0.139	3.1	0.247	5.4	0.461	10.2
D	80	2.82	0.282	10.0	0.184	6.5	0.068	2.4	0.343	12.2
E	80	0.99	0.099	10.0	0.000	0.0	0.037	3.8	0.105	10.7
F	80	0.63	0.064	10.2	0.013	2.0	0.017	2.8	0.067	10.7
G	80	0.23	0.031	13.5	0.012	5.3	0.000	0.0	0.034	14.6
NC	80	0.21	0.034	16.1	0.000	0.0	0.012	5.6	0.035	17.0
PC	80	4.15	0.306	7.4	0.000	0.0	0.143	3.4	0.337	8.1

Panel Member	Total No. Reps	Grand Mean (Rate)	Within-Run		BetweenRun		Between-Day		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
IC	80	93.76	8.811	9.4	0.000	0.0	5.181	5.5	10.221	10.9

Reproducibility has not been established for specimens containing the following anticoagulants: EDTA, heparin, sodium citrate, and potassium oxalate. The sponsor states in the labeling that the user is responsible for establishing assay reproducibility when using these matrices.

IX. Summary of Clinical Investigation

The objective of this clinical study was to assess the efficacy of AxSYM Anti-HCV for detecting anti-HCV antibodies in human serum or plasma as presumptive evidence of HCV infection. The following performance characteristics were studied:

Assay reactivity was evaluated by testing retrospective specimens which included previously characterized populations of HCV positive specimens, populations known to be at increased risk for HCV infection, HCV seroconversion panels, and HCV genotype panel.

Assay non-reactivity was evaluated by testing prospective specimens which included specimens from random volunteer whole blood donors, first-time volunteer whole blood donors, and random hospital patients, and by testing retrospective specimens which included patients with disease states other than HCV and specimens containing potentially interfering substances. Performance of AxSYM Anti-HCV was compared to the current Abbott HCV EIA 2.0 with regards to reactivity and non-reactivity based upon clinical specimen testing.

Clinical utility of the ASYM Anti-HCV assay was assessed by testing specimens from hospital patients with physicians' orders for hepatitis testing.

Clinical evaluation of AxSYM Anti-HCV was conducted at seven sites. However, not all sites conducted the same studies. The utility of AxSYM Anti-HCV for the qualitative detection of anti-HCV in human serum and plasma was determined by measuring precision, sensitivity, and specificity. One of the seven clinical sites tested specimens from patients with physicians' orders for hepatitis testing and four of the seven sites evaluated the prevalence of anti-HCV in first-time volunteer whole blood donors. The seven clinical sites included a hospital laboratory, a plasmapheresis center, two blood research laboratories, a university medical center laboratory, a reference laboratory, and Abbott Laboratories. A total of 5,623 clinical specimens were tested. Four AxSYM Anti-HCV reagent master lots were used in the evaluations, and the comparative assay was the FDA-approved Abbott HCV EIA 2.0. Testing was performed according to the AxSYM Anti-HCV assay clinical protocol/ brochure and the Abbott HCV EIA 2.0 package insert. All reactive specimens and AxSYM Anti-HCV gray zone specimens ($S/CO = 0.80$ to 1.20) were tested by a FDA-approved supplemental strip immunoblot assay (supplemental assay).

Prevalence

In order to evaluate the prevalence of anti-HCV detected by AxSYM Anti-HCV, random populations of hospital patients, first-time volunteer whole blood donors, and volunteer whole blood donors were tested. Two sites tested a total of 1,003 specimens from random hospital patients. Thirty-seven (3.7%) of the 1,003 random hospital patient specimens were reactive by AxSYM Anti-HCV. Twenty-nine (78.4%) of the 37 specimens were positive by the supplemental assay and considered to be positive for the presence of anti-HCV. Four specimens were repeatedly in the gray zone by AxSYM Anti-HCV and were excluded from the calculations. The estimated prevalence of anti-HCV detected by AxSYM Anti-HCV in a population of random hospital patients was 2.9% (29/999) with a 95% confidence interval of 2.0 to 4.1% by the binomial distribution. This prevalence is notably higher than the normal population.

Four sites tested a total of 2,508 specimens from first-time volunteer whole blood donors. Seventy-one (2.8%) of the 2,508 first-time volunteer whole blood donor specimens were reactive by AxSYM Anti-HCV. Sixty (84.5%) of the 71 specimens were positive by the supplemental assay and considered to be positive for the presence of anti-HCV. Three specimens were repeatedly in the gray zone by AxSYM Anti-HCV and were excluded from the calculations. The estimated prevalence of anti-HCV detected by AxSYM Anti-HCV in a population of first-time volunteer whole blood donors was 2.4% (60/2,505) with a 95% confidence interval of 1.8% to 3.1% by the binomial distribution.

Two sites tested a total of 1,006 random volunteer whole blood donors; one (0.1%) of the 1,006 random volunteer whole blood donor specimens was reactive by AxSYM Anti-HCV. This specimen was nonreactive by the supplemental assay and considered to be negative for the presence of anti-HCV. One specimen was repeatedly in the gray zone by AxSYM Anti-HCV and was excluded from the calculations. The estimated prevalence of anti-HCV detected by AxSYM Anti-HCV in a population of random volunteer whole blood donors was 0% (0/1,005) with a 95% confidence interval of 00.0 to 00.4% by the binomial distribution.

Reactivity (Percent Agreement Positive)

The data in Table 6 are not the basis for claiming performance of AxSYM Anti-HCV in any particular population. While the data for different categories of individuals (including types of characterized HCV infections) are descriptive of populations that were studied, it is not known if the type of HCV infection or

associated diseases affects performance of AxSYM Anti-HCV, particularly with regard to effects that might be different from those on performance of other current assays that presumptively detect anti-HCV.

Table 6 presents AxSYM Anti-HCV results for 679 specimens, each representing an individual pertinent to AxSYM Anti-HCV intended use. All of these specimens were characterized by testing for anti-HCV and reference assays. Those specimens that contain anti-HCV were defined by reactive results with Abbott HCV EIA 2.0, that uses the same antigens as AxSYM Anti-HCV: core, 33c, c200, and c100-3, and with an FDA-approved strip immunoblot assay that uses similar antigens: c22 representing core, 33c, c100-3, and 5.1.1 representing NS4. Specimens not shown to contain anti-HCV were defined by any of the following patterns of results: HCV EIA 2.0 nonreactive, HCV EIA 2.0 reactive and immunoblot-nonreactive, or HCV EIA 2.0 reactive and immunoblot-indeterminate. AxSYM Anti-HCV results were analyzed for reactivity (AxSYM Anti-HCV-non-reactive results among specimens not shown to contain anti-HCV).

Percent Agreement Positive and Percent Agreement Negative between AxSYM Anti-HCV and the Abbott HCV EIA 2.0 and the strip immunoblot assay were calculated and 95 percent confidence intervals (95% CI) were obtained. These results are exhibited in Table 6.

TABLE 6
% Agreement of AxSYM Anti-HCV[#]

Category	Number of Specimens Tested	% Agreement Positive (95% Confidence Interval)	% Agreement Negative (95% Confidence Interval)
Characterized HCV Infection [†]	157	157/157 (100.0%) (97.7 - 100.0)	
Individuals with Anti-HCV [‡]	273	273/273 (100.0%) (98.7 - 100.0)	
Hospital Patients with Physicians' Orders for Hepatitis Testing	99	5/5 (100.0%) (47.8 - 100.0)	93/94 (98.9%) (94.2 - 100.0)
Individuals at Increased Risk:			
- Hemodialysis Patients	50	26/26 (100.0%) (86.8 - 100.0)	16/24 [§] (66.7%) (44.7 - 84.4)
- Hemophilia Patients	50	50/50 (100.0%) (92.9 - 100.0)	
- Injection Drug Users	50	15/15 (100.0%) (78.2 - 100.0)	35/35 (100.0%) (90.0 - 100.0)

[#] Information about age and gender for individual is not available

[†] Characterized infections include 33 acute (15 seroconversions and 18 with jaundice or high aminotransferase levels and with other likely causes excluded), 24 chronic (anti-HCV detected for ≥ 6 months and one or more among histopathologic evidence of chronic hepatitis, treatment with interferon, or detectable HCV RNA), and 100 asymptomatic (identified as HCV-infected during donor screening). Tested specimens were selected from frozen collections and did not represent random samples of the studied populations.

[‡] Insufficient information to enable determination of the state of HCV infection.

[§] AxSYM Anti-HCV results for these 24 specimens: 16 nonreactive, 6 reactive, and 2 equivocal.

Characterized HCV Infection

In order to determine Percent Agreement Positive, three clinical sites evaluated a total of 157 specimens from individuals who were clinically classified as being asymptomatic, with acute or chronic HCV infection. One hundred specimens were from normal, healthy blood donors who had asymptomatic HCV infection at the time of donation. Thirty-three specimens were from individuals with acute HCV infection; these included 15 seroconversions and 18 with jaundice or high aminotransferase levels. The remaining 24 specimens were from individuals who were clinically and serologically diagnosed with chronic HCV infection. Percent Agreement Positive of AxSYM Anti-HCV was estimated to be 100.00% (157/157) with a 95% confidence interval of 97.7% to 100.0% by the binomial distribution.

HCV RNA was detected in 11 of the 15 seroconversion panels. There were no HCV RNA results for the remaining four panels. Detection of anti-HCV by AxSYM Anti-HCV was coincident with HCV EIA 2.0 in 5 of the 15 seroconversion panels. AxSYM Anti-HCV detected anti-HCV earlier than HCV EIA 2.0 in 9 of the 15 seroconversion panels. HCV EIA 2.0 detected anti-HCV one bleed earlier than AXSYM Anti-HCV in one seroconversion panel.

HCV Genotypes

A study was done to determine if AxSYM Anti-HCV could yield reactive results during infections with different variants of HCV. One hundred twenty-seven specimens were characterized by testing for anti-HCV with reference assays (as described above in Table 6) and by research methods for determining genotype or subtype (restriction fragment length polymorphism, line probe assay, sequence analysis of 5' nontranslated or core regions, or primer-specific polymerase chain reaction). The geographic origins of these specimens were North America, Central America, Africa, and Asia. Anti-HCV was detected in 125 specimens. Genotype or subtype was determined for all 127 specimens as 1a, 1b, 2a, 2b, 3, 3a, 4, 5, or 6a; subtype and genotype were respectively 2b and 5 for the 2 specimens shown not to contain anti-HCV. AxSYM results were reactive for 100% of the 125 specimens with anti-HCV and nonreactive for the 2 specimens shown not to contain anti-HCV. These data are suggestive of AxSYM Anti-HCV reactivity for a broad range of HCV variants but, because the accuracy of the genotyping methods is not known, and because the assay detects antibodies to HCV, it is not possible to determine any anti-HCV assay's effectiveness among all HCV variants.

X. CONCLUSIONS DRAWN FROM THE STUDIES

The data from the non-clinical studies demonstrated acceptable analytical sensitivity and specificity, reproducibility, and stability of the AxSYM Anti-HCV when used according to the instructions for use as stated in the labeling, the warnings and precautions, and the Specimen Collection and Preparation for Analysis and Limitations section of the labeling.

The clinical studies in this application indicate that the AxSYM Anti-HCV assay is safe and effective when used according to the directions for use in the labeling. The sponsor has provided scientific data to support the utility of this assay in conjunction with other laboratory results and clinical information as an aid in the diagnosis of HCV associated disease.

Risk Benefit Analysis

The nonclinical and clinical studies contained in this application demonstrated that the device is safe and effective as indicated. It can therefore be concluded that the benefits of the AxSYM Anti-HCV, when used according to the provided directions and in conjunction with other serological and clinical information outweigh any risk that may be associated with its use.

XI. PANEL RECOMMENDATION

On January 21, 2000, the Microbiology Devices Advisory Panel recommended that the PMA be approved with conditions.

The following approval conditions were stipulated:

1. Inclusion of a narrative below the intended use statement that repeat reactives should be retested by a supplemental assay.
2. Inclusion in the package insert that performance characteristics data are descriptive of the population studies but are not intended to be representative of any particular disease states. Test results are intended to provide an assessment of antibody status but individual diagnosis should be made only in the context of clinical information and other laboratory parameters.
3. Sub-division of "Individuals at Increased Risk" populations by individual groups, that is, dialysis patients, etc.
4. Under the Interpretation of results section, inclusion of the following sentence: "A non-reactive anti-HCV result does not exclude infection with HCV".

XII. CDRH DECISION

CDRH concurred with the panel's recommendation. The sponsor made the labeling changes as recommended by the Panel. CDRH issued an approvable letter dated March 24, 2000, pending the satisfactory compliance with the Quality System Regulation (21 CFR Part 820) as documented in the November 2, 1999, consent decree. The applicant's manufacturing and control facilities were inspected on October 28-November 13, 2003, and the facilities were found to be in compliance with the Quality System Regulations on December 18, 2003. Abbott's AxSYM® Anti-HCV was approved on February 5, 2004.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See attached labeling.

Hazards to Health from use of Device: See Indications, Contraindications, Warnings and Precautions and Adverse Events in the labeling.

Conditions of Approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the approval order.

Post-approval Requirements and Restrictions: See Approval Order